pai Pharmaceutical Associates, Inc.

April 6, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Room 4-62
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this Petition, pursuant to Section 505(j)(2)(c) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 C.F.R. Sections 314.93(b) and 10.30 of the Food and Drug Administration's regulations, to request the Commissioner of Food and Drugs to make a determination that a certain opioid analgesic elixir drug product is suitable for filing under an abbreviated new drug application (ANDA).

A. Action Requested

Petitioner requests that the Commissioner of Food and Drugs make a determination that an abbreviated new drug application (ANDA) is suitable for elixirs containing 10 mg hydrocodone bitartrate/325 mg acetaminophen per 15 mL, 10 mg hydrocodone bitartrate/500 mg acetaminophen per 15 mL, and 10 mg hydrocodone bitartrate/650 mg acetaminophen per 30 mL.

B. Statement of Grounds

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Waxman-Hatch Act") extends eligibility for the submission of ANDA's to certain drug products identical to those approved via new drug applications, as identified in the *List of Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") published by the Food and Drug Administration. Where the proposed drug product differs from the "listed drug" in one or more respects, a person may petition the Agency, under section 505(j)(2)(c) of the Act, for a determination that the proposed drug is suitable to be submitted as an ANDA.

The listed drug product that forms the basis for this petition Norco™,10 mg/325 mg,(ANDA 40-148, manufactured by Watson Labs) Watson 10 mg/500 mg, (ANDA 40-148) Watson,10 mg/650 mg (ANDA 40-094). See Orange Book, page 3-4 and 3-3, at Exhibit A. To the best of petitioner's knowledge, applicable U.S. patents with respect to the drug substances, hydrocodone bitartrate and acetaminophen, have expired.

Beach Products, Inc./Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (813) 839-6565
Fax: (813) 837-2511

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Pharmaceutical Associates Subsidiary
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

The proposed drug product differs from the listed drug products only in regard to dosage form (elixir instead of tablet). Otherwise, the proposed drug product is identical with respect to active ingredients, strength, route of administration, and conditions of use.

The availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen would provide a valuable dosage alternative, particularly for those patients who have trouble swallowing tablets, the geriatric population and other situations where a liquid dosage would be preferred.

The proposed product's dosage form is the same as several other types of approved opioid analgesic drugs which are available in liquid form. For instance, Capital and Codeine (acetaminophen and codeine), NDA 85883 (*Orange Book* at 3-2); Dilaudid (hydromorphone hydrochloride), NDA 19891 (*Orange Book* at 3-182); and Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), ANDA 81051 (*Orange Book* at 3-4) attached as Exhibit B.

In view of the availability of other approved opioid analgesics as elixirs and an appropriate patient base for such a form (e.g., geriatric patients), the healthcare community would benefit from the availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 gm per 15mL, and 10 mg/650 mg per 30 mL. The proposed product contains the same active ingredients, at the same strength and route of administration, and would be labeled with the same conditions of use as the listed 10 mg/325 mg, 10 mg/500 mg, and 10mg/650 mg tablets [See Exhibits C (Side-By-Side comparison of Watson and Norco inserts and proposed insert) and D (Side-By-Side comparison of Watson and Norco labeling and proposed labeling)] and packaged in an appropriate container-closure system (See Exhibit E).

Based on the foregoing, Petitioner believes that an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 gm per 15mL, and 10 mg/650 mg per 30 mL warrants a finding of ANDA suitability and that the commissioner should grant permission for the filing of an ANDA for a hydrocodone bitartrate and acetaminophen elixir in the strengths of 10 mg/325 mg per 15 mL, 10 mg/500 mg per mL, and 10mg/650 mg per 30 mL.

C. Environmental Impact

A categorical exclusion is claimed as the granting of this Petition will result in an ANDA for a drug product that is consistent with the parameters for exclusion established in 21 C.F.R. 25.24(c)(1).

D. Economic Impact

Information under this section will be submitted if requested by the Commissioner following review of this Petition.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views upon which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

PHARMACEUTICAL ASSOCIATES, INC.

By: Kaye B. McDonald

Kaye B. McDonald
201 Delaware Street
Greenville, SC 29605
(864) 277-7282 Ext. 230

Enclosures:

A. *Orange Book*, page 3-5.

B. *Orange Book*, pages 3-2, 3-4, and 3-182.

C. Side-By-Side comparison of Watson and Norco™ package insert (May 1998 and December 1997) and proposed insert.

D. Side-By-Side comparison of Watson and Norco™ and labeling and proposed labeling for hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 mg per 15 mL, and 10 mg/650 mg per 30 mL elixir.

E. Description of container and closure system for hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 mg per 15 mL, and 10 mg/650 mg per 30 mL elixir.

Exhibit A

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

		HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
AA		VINTAGE PHARMS	650MG;10MG	**N40143 001** FEB 22, 1996
AA			750MG;7.5MG	**N40157 001** APR 12, 1996
AA		WATSON LABS	500MG;2.5MG	**N40123 003** MAR 04, 1996
AA			500MG;2.5MG	**N81079 001** AUG 30, 1991
AA			500MG;5MG	**N40122 001** MAR 04, 1996
AA			500MG;5MG	**N89883 001** DEC 01, 1988
AA			500MG;7.5MG	**N40123 004** MAR 04, 1996
AA			500MG;7.5MG	**N81080 001** AUG 30, 1991
AA			500MG;10MG ✓	**N40148 002** FEB 14, 1997
AA			650MG;7.5MG	**N40094 001** SEP 29, 1995
AA			650MG;7.5MG	**N40123 001** MAR 04, 1996
AA			650MG;10MG ✓	**N40094 002** SEP 29, 1995
AA			650MG;10MG	**N40123 002** MAR 04, 1996
AA			750MG;7.5MG	**N40122 002** MAR 04, 1996
AA			750MG;7.5MG	**N81083 001** AUG 30, 1991
AA		ZENITH GOLDLINE	500MG;5MG	**N89696 001** APR 21, 1988
		LORTAB		
AA		MALLINCKRODT	500MG;5MG	**N87722 001** JUL 09, 1982
AA	+	UCB	500MG;10MG	**N40100 001** JAN 26, 1996
			325MG;5MG	N40099 001 JUN 25, 1997
		NORCO		
	+	WATSON LABS	325MG;10MG ✓	N40148 001 FEB 14, 1997
		VICODIN		
AA	+	KNOLL PHARM	500MG;5MG	**N88058 001** JAN 07, 1983

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

		VICODIN ES		
AA	+	KNOLL PHARM	750MG;7.5MG	**N89736 001** DEC 09, 1988
		VICODIN HP		
AA		KNOLL PHARM	660MG;10MG	**N40117 001** SEP 23, 1996

ACETAMINOPHEN; OXYCODONE

CAPSULE; ORAL

		OXYCODONE AND ACETAMINOPHEN		
AA		HALSEY	500MG;5MG	**N40219 001** JAN 22, 1998

ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE

CAPSULE; ORAL

		OXYCODONE AND ACETAMINOPHEN		
AA		AMIDE PHARM	500MG;5MG	**N40199 001** DEC 30, 1998
AA		MALLINCKRODT	500MG;5MG	**N40257 001** AUG 04, 1998
AA		VINTAGE PHARMS	500MG;5MG	**N40106 001** JUL 30, 1996
AA		WATSON LABS	500MG;5MG	**N40234 001** OCT 30, 1997
		ROXILOX		
AA		ROXANE	500MG;5MG	**N40061 001** JUL 03, 1995
		TYLOX		
AA	+	JOHNSON RW	500MG;5MG	**N88790 001** DEC 12, 1984

SOLUTION; ORAL

		ROXICET		
		ROXANE	325MG/5ML;5MG/5ML	N89351 001 DEC 03, 1986

TABLET; ORAL

		OXYCET		
AA		MALLINCKRODT	325MG;5MG	**N87463 001** DEC 07, 1983
		OXYCODONE AND ACETAMINOPHEN		
AA		DURAMED	325MG;5MG	**N40272 001** JUN 30, 1998

Exhibit B

ACETAMINOPHEN; BUTALBITAL; CAFFEINE

CAPSULE; ORAL

	ANOQUAN				
AB	ROBERTS AND HAUCK	325MG;50MG;40MG	N87628 001	OCT 01, 1986	
	BUTALBITAL, ACETAMINOPHEN AND CAFFEINE				
AB	WEST WARD	500MG;50MG;40MG	N40261 001	OCT 28, 1998	
	BUTALBITAL, ACETAMINOPHEN, CAFFEINE				
AB	GRAHAM DM	325MG;50MG;40MG	N88758 001	MAR 27, 1985	
	ESGIC-PLUS				
AB	+ MIKART	500MG;50MG;40MG	N40085 001	MAR 28, 1996	
	FEMCET				
AB	MALLINCKRODT	325MG;50MG;40MG	N89102 001	JUN 19, 1985	
	TRIAD				
AB	MALLINCKRODT	325MG;50MG;40MG	N89023 001	JUN 19, 1985	

TABLET; ORAL

	BUTALBITAL, ACETAMINOPHEN AND CAFFEINE				
AB	MALLINCKRODT	325MG;50MG;40MG	N87804 001	JAN 24, 1985	
AB	MIKART	325MG;50MG;40MG	N89175 001	JAN 21, 1987	
AB	+	500MG;50MG;40MG	N89451 001	MAY 23, 1988	
AB	WATSON LABS	500MG;50MG;40MG	N40267 001	JUL 30, 1998	
AB	WEST WARD	325MG;50MG;40MG	N89718 001	JUN 12, 1995	
	BUTALBITAL, APAP, AND CAFFEINE				
AB	HALSEY	325MG;50MG;40MG	N89536 001	FEB 16, 1988	
	FIORICET				
AB	+ NOVARTIS	325MG;50MG;40MG	N88616 001	NOV 09, 1984	

ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE

CAPSULE; ORAL

	FIORICET W/ CODEINE				
	+ NOVARTIS	325MG;50MG;40MG;30MG	N20232 001	JUL 30, 1992	

ACETAMINOPHEN; CAFFEINE; DIHYDROCODEINE BITARTRATE

CAPSULE; ORAL

	ACETAMINOPHEN, CAFFEINE, AND DIHYDROCODEINE BITARTRATE				
AA	MIKART	356.4MG;30MG;16MG	N40109 001	AUG 26, 1997	
	DHC PLUS				
AA	+ PURDUE FREDERICK	356.4MG;30MG;16MG	N88584 001	MAR 04, 1986	

ACETAMINOPHEN; CODEINE PHOSPHATE

CAPSULE; ORAL

	PHENAPHEN W/ CODEINE NO. 2				
	+ ROBINS AH	325MG;15MG	N84444 001		
	PHENAPHEN W/ CODEINE NO. 3				
	+ ROBINS AH	325MG;30MG	N84445 001		
	PHENAPHEN W/ CODEINE NO. 4				
	+ ROBINS AH	325MG;60MG	N84446 001		

SOLUTION; ORAL

	ACETAMINOPHEN AND CODEINE PHOSPHATE				
AA	ALPHARMA	120MG/5ML;12MG/5ML	N85861 001		
AA	HI TECH PHARMA	120MG/5ML;12MG/5ML	N40119 001	APR 26, 1996	
AA	MIKART	120MG/5ML;12MG/5ML	N89450 001	OCT 27, 1992	
AA	MORTON GROVE	120MG/5ML;12MG/5ML	N87006 001		
AA	MOVA	120MG/5ML;12MG/5ML	N40098 001	SEP 20, 1996	
AA	PHARM ASSOC	120MG/5ML;12MG/5ML	N87508 001		
	ACETAMINOPHEN W/ CODEINE				
AA	ROXANE	120MG/5ML;12MG/5ML	N86366 001		
	TYLENOL W/ CODEINE				
AA	+ JOHNSON RW	120MG/5ML;12MG/5ML	N85057 001		

SUSPENSION; ORAL

	ACETAMINOPHEN AND CODEINE PHOSPHATE				
AA	CARNRICK	120MG/5ML;12MG/5ML	N86024 001		
	CAPITAL AND CODEINE				
AA	ALPHARMA	120MG/5ML;12MG/5ML	N85883 001		

TABLET; ORAL

	ACETAMINOPHEN AND CODEINE PHOSPHATE				
AA	DURAMED	300MG;15MG	N40223 001	NOV 18, 1997	
AA		300MG;30MG	N40223 002	NOV 18, 1997	

ACETAMINOPHEN; HYDROCODONE BITARTRATE

ELIXIR; ORAL

		HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
AA	+ MIKART	500MG/15ML;7.5MG/15ML	✓ N81051 001	AUG 28, 1992
		500MG/15ML;5MG/15ML	N81226 001	OCT 27, 1992
		500MG/15ML;5MG/15ML	N89557 001	APR 29, 1992
	+			
AA	PHARM ASSOC	500MG/15ML;7.5MG/15ML	N40182 001	MAR 13, 1998

TABLET; ORAL

	ANEXSIA			
AA	MALLINCKRODT	500MG;5MG	N89160 001	APR 23, 1987
	ANEXSIA 10/660			
AA	+ MALLINCKRODT	660MG;10MG	N40084 003	JUL 29, 1996
	ANEXSIA 7.5/650			
AA	MALLINCKRODT	650MG;7.5MG	N89725 001	SEP 30, 1987
	CO-GESIC			
AA	SCHWARZ PHARMA	500MG;5MG	N87757 001	MAY 03, 1982
	HY-PHEN			
AA	ASCHER	500MG;5MG	N87677 001	MAY 03, 1982
	HYDROCODONE BITARTRATE AND ACETAMINOPHEN			
AA	ENDO PHARMS	500MG;5MG	N40281 001	SEP 30, 1998
AA		500MG;7.5MG	N40280 001	SEP 30, 1998
AA		650MG;7.5MG	N40280 002	SEP 30, 1998
AA		650MG;10MG	N40280 003	SEP 30, 1998
AA		750MG;7.5MG	N40281 002	SEP 30, 1998
		400MG;5MG	N40288 001	NOV 27, 1998
		400MG;7.5MG	N40288 002	NOV 27, 1998
		400MG;10MG	N40288 003	NOV 27, 1998
AA	EON	500MG;5MG	N40149 001	JAN 27, 1997

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

		HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
AA	EON	750MG;7.5MG	N40149 002	JAN 27, 1997
AA	HALSEY	500MG;5MG	N40236 001	SEP 25, 1997
AA		650MG;7.5MG	N40240 002	NOV 26, 1997
AA		650MG;10MG	N40240 001	NOV 26, 1997
AA		750MG;7.5MG	N40236 002	SEP 25, 1997
AA	MALLINCKRODT	500MG;5MG	N40084 002	JUN 01, 1995
AA		500MG;7.5MG	N40201 001	FEB 27, 1998
AA		500MG;10MG	N40201 002	FEB 27, 1998
AA		750MG;7.5MG	N40084 001	JUN 01, 1995
AA	+ MIKART	500MG;2.5MG	N89698 001	AUG 25, 1989
AA		500MG;5MG	N89271 001	JUL 16, 1986
AA		500MG;5MG	N89697 001	JAN 28, 1992
AA	+	500MG;7.5MG	N89699 001	AUG 25, 1989
AA	+	650MG;7.5MG	N89689 001	JUN 29, 1988
AA	+	650MG;10MG	N81223 001	MAY 29, 1992
AA	PEACHTREE	500MG;10MG	N40210 001	AUG 13, 1997
AA	UCB	650MG;7.5MG	N40134 001	NOV 21, 1996
AA	VINTAGE PHARMS	500MG;2.5MG	N40144 002	APR 25, 1997
AA		500MG;5MG	N89831 001	SEP 07, 1988
AA		500MG;5MG	N89971 001	DEC 02, 1988
AA		500MG;7.5MG	N40144 001	FEB 22, 1996
AA		650MG;7.5MG	N40155 001	APR 14, 1997

HYDROCORTISONE SODIUM SUCCINATE

INJECTABLE; INJECTION
SOLU-CORTEF

AP	+	PHARMACIA AND UPJOHN	EQ 500MG BASE/VIAL	N09866 003
AP	+		EQ 1GM BASE/VIAL	N09866 004

HYDROCORTISONE VALERATE

CREAM; TOPICAL
HYDROCORTISONE VALERATE

AB		COPLEY PHARM	0.2%	N74489 001 AUG 12, 1998
AB		TARO	0.2%	N75042 001 AUG 25, 1998

WESTCORT

AB	+	WESTWOOD SQUIBB	0.2%	N17950 001

OINTMENT; TOPICAL
HYDROCORTISONE VALERATE

AB		TARO	0.2%	N75043 001 AUG 25, 1998

WESTCORT

AB	+	WESTWOOD SQUIBB	0.2%	N18726 001 AUG 08, 1983

HYDROFLUMETHIAZIDE

TABLET; ORAL
DIUCARDIN

AB		WYETH AYERST	50MG	N83383 001

HYDROFLUMETHIAZIDE

AB		PAR PHARM	50MG	N88850 001 MAY 31, 1985

SALURON

AB	+	ROBERTS LABS	50MG	N11949 001

HYDROFLUMETHIAZIDE; RESERPINE

TABLET; ORAL
RESERPINE AND HYDROFLUMETHIAZIDE

BP		PAR PHARM	50MG;0.125MG	N88907 001 SEP 20, 1985

SALUTENSIN

BP	+	ROBERTS LABS	50MG;0.125MG	N12359 003

SALUTENSIN-DEMI

		ROBERTS LABS	25MG;0.125MG	N12359 004

HYDROMORPHONE HYDROCHLORIDE

INJECTABLE; INJECTION
DILAUDID-HP

AP	+	KNOLL PHARM	10MG/ML	N19034 001 JAN 11, 1984
	+		250MG/VIAL	N19034 002 AUG 04, 1994

HYDROMORPHONE HCL

AP		ABBOTT	10MG/ML	N74598 001 JUN 19, 1997
AP		STERIS	10MG/ML	N74317 001 AUG 23, 1995

SOLUTION; ORAL
DILAUDID

AA	+	KNOLL PHARM	5MG/5ML	N19891 001 DEC 07, 1992

HYDROMORPHONE HCL

AA		ROXANE	5MG/5ML	N74653 001 JUL 29, 1998

TABLET; ORAL
DILAUDID

AB	+	KNOLL PHARM	8MG	N19892 001 DEC 07, 1992

HYDROMORPHONE HCL

AB		ROXANE	8MG	N74597 001 JUL 29, 1998

HYDROXOCOBALAMIN

INJECTABLE; INJECTION
HYDROXOCOBALAMIN

	+	STERIS	1MG/ML	N85998 001

HYDROXYAMPHETAMINE HYDROBROMIDE

SOLUTION/DROPS; OPHTHALMIC
PAREDRINE

	+	PHARMICS	1%	N00004 004

Exhibit C

We are proposing two formulas for the
Hydrocodone Bitartrate and Acetaminophen Elixir 10/325.
One will have blue dye and the other will be dye-free.

ANDA Product

Listed Drug

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate and acetaminophen in the following strengths per 15 mL:

Hydrocodone Bitartrate, USP	10 mg
Acetaminophen, USP	325 mg

In addition, the elixir contains the following inactive ingredients: Alcohol, 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, and Mixed Fruit Flavor.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak

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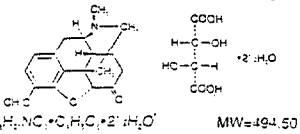
NORCO® TABLETS

DESCRIPTION

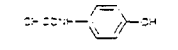
NORCO® (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW=151.17

Each NORCO® tablet contains:

Hydrocodone Bitartrate (WARNING: May be habit forming)	10 mg
Acetaminophen	325 mg

[redacted] magnesium stearate, microcrystalline cellulose, pregelatinized starch, stearic acid.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels

= Brand Name / Generic Name

[redacted] = Change due to dosage form

ANDA Product

concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Listed Drug

achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See **OVERDOSAGE** for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

NORCO® Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

NORCO® Tablets should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

= Brand Name / Generic Name

ANDA Product

General: Special Risk Patients: As with any opioid analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Listed Drug

General: Special Risk Patients: As with any narcotic analgesic agent, NORCO® Tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough reflex: Hydrocodone suppresses the cough reflex as with all narcotics, caution should be exercised when NORCO® Tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: NORCO® Tablets, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or *operating machinery; patients should be cautioned accordingly.*

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: *Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents,* or other CNS depressants (including alcohol) concomitantly with NORCO® Tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

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Pregnancy:

= Brand Name / Generic Name

ANDA Product

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in peciatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Listed Drug

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NORCO® Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to deliver will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

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Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

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Gastrointestinal System: Prolonged administration of NORCO® Tablets may produce constipation.

= Name Brand/
Generic Name

ANDA Product

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:
Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Listed Drug

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

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DRUG ABUSE AND DEPENDENCE

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Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme

= Brand Name / Generic Name

ANDA Product

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 – 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Listed Drug

somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

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ANDA Product

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful (15 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a clear, slightly, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 325 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied as follows:

10mg/325mg per 15 mL	
16 oz. Bottles	NDC 0121-0715-16
4 oz. Bottles	NDC 0121-0715-04
15 mL Unit Dose Cups	NDC 0121-0715-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC

02/00

Listed Drug

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Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

NORCO® is supplied as a yellow, capsule-shaped tablet containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen, bisected on one side and debossed with "NORCO 539" on the other side.

Bottles of 100	NDC 52544-539-01
Bottles of 500	NDC 52544-539-05

Store at controlled room temperature. 15° - 30°C (59°- 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

Rx only

WATSON PHARMA
A Division of Watson Laboratories, Inc.
Corona, CA 91720

Revised May 15, 1998
13095-1

= Brand Name / Generic Name

[redacted] = change due to dosage form

"Controlled Room Temperature" changed to current USP 24

ANDA Product

Listed Drug

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate and acetaminophen in the following strengths per 15 mL:

Hydrocodone Bitartrate, USP	10 mg
Acetaminophen, USP	325 mg

In addition, the elixir contains the following inactive ingredients: Alcohol, 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, Mixed Fruit Flavor, and FD&C Blue No. 1.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

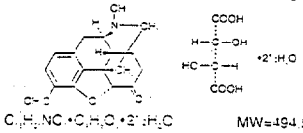
The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

NORCO® TABLETS C

DESCRIPTION

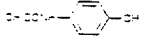
NORCO® (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW=151.17

Each NORCO® tablet contains:

Hydrocodone Bitartrate (WARNING: May be habit forming)	10 mg
Acetaminophen	325 mg

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, [illegible].

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

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= Name Brand / Generic Name

[redacted] = Change due to dosage form

ANDA Product

Listed Drug

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

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= Brand Name / Generic Name

ANDA Product

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any opioid analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to

Listed Drug

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

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Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

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The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for

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ANDA Product

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determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:
Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NORCO® Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of NORCO® Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

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Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:
Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

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Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Listed Drug

Gastrointestinal System: Prolonged administration of NORCO® Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

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Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, NORCO® Tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when NORCO® Tablets are used for a short time for the treatment of pain.

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OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms

= Brand Name / Generic Name

ANDA Product

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 – 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be

Listed Drug

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed

ANDA Product

administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful (15 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a blue-colored, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 325 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied as follows:

10mg/325mg per 15 mL	
16 oz. Bottles	NDC 0121-0716-16
4 oz. Bottles	NDC 0121-0716-04
15 mL Unit Dose Cups	NDC 0121-0716-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC

02/00

Listed Drug

to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

NORCO® is supplied as a yellow, capsule-shaped tablet containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen, bisected on one side and debossed with "NORCO 539" on the other side.

Bottles of 100	NDC 52544-539-01
Bottles of 500	NDC 52544-539-05

Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

Rx only

WATSON PHARMA
A Division of Watson Laboratories, Inc.
Corona, CA 91720

Revised May 15, 1998
13095-1

= Brand Name / Generic

= change due to dosage form

= Controlled Room Temperature changed to current USP 24

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HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate and acetaminophen in the following strengths per 15 mL:

Hydrocodone Bitartrate, USP	10 mg
Acetaminophen, USP	500 mg

In addition, the elixir contains the following inactive ingredients: Alcohol, 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, and Mixed Fruit Flavor, FD&C Yellow No. 10 and FD&C Blue No. 1.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

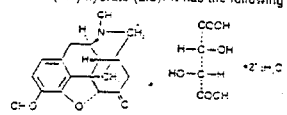
Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone Bitartrate
(Warning: May be habit forming)
and
Acetaminophen Tablets, USP CIII

DESCRIPTION

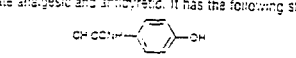
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white cry or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



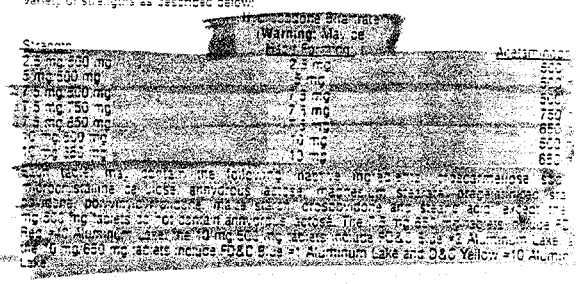
$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW=151.17

Hydrocodone Bitartrate and Acetaminophen Tablets, USP for oral administration are available variety of strengths as described below:



Strength	Hydrocodone Bitartrate (Warning: May be Habit Forming)	Acetaminophen
2.5 mg/300 mg	2.5 mg	300
5 mg/300 mg	5 mg	300
7.5 mg/300 mg	7.5 mg	300
7.5 mg/500 mg	7.5 mg	500
7.5 mg/650 mg	7.5 mg	650
10 mg/300 mg	10 mg	300
10 mg/500 mg	10 mg	500
10 mg/650 mg	10 mg	650

Each tablet contains the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, colloidal silicon dioxide, stearic acid, sodium starch glycolate and talc. In addition, the 2.5 mg/300 mg tablets also contain anhydrous lactose. The 5 mg/300 mg, 7.5 mg/300 mg, 7.5 mg/500 mg, 7.5 mg/650 mg, 10 mg/300 mg, 10 mg/500 mg and 10 mg/650 mg tablets also contain FD&C Blue #1 Aluminum Lake and D&C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

= Brand Name / Generic Name

= change due to dosage form

ANDA Product

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

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Listed Drug

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See OVERDOSAGE for toxicity information

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See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen tablets are indicated for the relief of moderate to moderat severe pain.

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WARNINGS

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Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis clinical course of patients with acute abdominal conditions.

ANDA Product

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PRECAUTIONS

General: Special Risk Patients: As with any opioid analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

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General: Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

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Pregnancy:

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Pregnancy:

Teratogenic Effects: Pregnancy, Category C. There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

= Brand Name / Generic Name

ANDA Product

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:
Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Listed Drug

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention h been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respira depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminop allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified a Schedule III controlled substance.

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OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depressio decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis; extre

= Brand Name |
Generic Name

ANDA Product

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 – 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Listed Drug

somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, a sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collap cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necro is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, a thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiti diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 gram or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentia lethal polydrug overdose, and consultation with a regional poison control center is recommende

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ANDA Product

Listed Drug

f the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour ntervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful (15 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a green-colored, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied as follows:

10mg/500 mg per 15 mL:	
16 oz. Bottles	NDC 0121-0717-16
1 oz. Bottles	NDC 0121-0717-04
15 mL Unit Dose Cups	NDC 0121-0717-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

℞ ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC

02/00

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

2.5 mg/500 mg	The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
5 mg/500 mg	The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
7.5 mg/500 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
7.5 mg/750 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.
7.5 mg/650 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
10 mg/500 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
10 mg/650 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in the following strengths:

2.5 mg/500 mg — 2.5 mg hydrocodone bitartrate and 500 mg acetaminophen, oblong, white tablets bisected on one side and debossed with Watson 383 on [illegible]

Bottles of 100 NDC 52544-383-01
Bottles of 500 NDC 52544-383-05
Bottles of 1000 NDC 52544-383-10

5 mg/500 mg — 5 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, [illegible] tablets bisected on one side and debossed with Watson 384 on the other side.

Bottles of 100 NDC 52544-384-01
Bottles of 500 NDC 52544-384-05
Bottles of 1000 NDC 52544-384-10

7.5 mg/500 mg — 7.5 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, [illegible] tablets bisected on one side and debossed with Watson 385 on the other side.

Bottles of 30 NDC 52544-385-30
Bottles of 100 NDC 52544-385-01
Bottles of 500 NDC 52544-385-05
Bottles of 1000 NDC 52544-385-10

7.5 mg/750 mg — 7.5 mg hydrocodone bitartrate and 750 mg acetaminophen, oblong, white tablets bisected on one side and debossed with Watson 387 on the other side.

Bottles of 30 NDC 52544-387-30
Bottles of 100 NDC 52544-387-01
Bottles of 500 NDC 52544-387-05
Bottles of 1000 NDC 52544-387-10

7.5 mg/650 mg — 7.5 mg hydrocodone bitartrate and 650 mg acetaminophen, capsule-shaped, pink tablets bisected on one side and debossed with Watson 502 on the other side.

Bottles of 100 NDC 52544-502-01
Bottles of 500 NDC 52544-502-05

10 mg/500 mg — 10 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, blue tablets bisected on one side and debossed with Watson 540 on the other side.

Bottles of 100 NDC 52544-540-01
Bottles of 500 NDC 52544-540-05

10 mg/650 mg — 10 mg hydrocodone bitartrate and 650 mg acetaminophen, capsule-shaped, light green tablets bisected on one side and debossed with Watson 503 on the other side.

Bottles of 100 NDC 52544-503-01
Bottles of 500 NDC 52544-503-05

Store at controlled room temperature 15° - 30°C (59° - 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

Watson Laboratories
Corona, CA 91720

Revised December 15, 1997
13100-1

= Brand Name / Generic Name

[redacted] = change due to dosage form

= Controlled Room Temperature changed to Current USP 24

ANDA Product

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate and acetaminophen in the following strengths per 30 mL:

Hydrocodone Bitartrate, USP	10 mg
Acetaminophen, USP	650 mg

In addition, the elixir contains the following inactive ingredients: Alcohol, 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, and Mixed Fruit Flavor.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

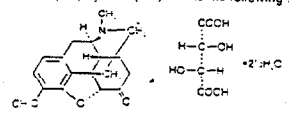
Listed Drug

Hydrocodone Bitartrate
(Warning: May be habit forming)
and
Acetaminophen Tablets, USP CIII

DESCRIPTION

Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

$C_8H_9NO_2$ MW=151.17

Hydrocodone Bitartrate and Acetaminophen Tablets, USP for oral administration are available in a variety of strengths as described below:

Hydrocodone Bitartrate

Strength	(Warning: May be Habit Forming)	Acetaminophen
[illegible]	2.5 mg	500 mg
[illegible]	5 mg	500 mg
[illegible]	7.5 mg	500 mg
[illegible]	7.5 mg	750 mg
[illegible]	7.5 mg	650 mg
[illegible]	10 mg	500 mg
[illegible]	10 mg	650 mg

[illegible] inactive ingredients [illegible] magnesium stearate, pregelatinized starch, [illegible] and stearic acid, except the [illegible] contain [illegible] dioxide. The 2.5 mg 500 mg tablets include [illegible] tablets include FD&C Blue #2 Aluminum Lake [illegible] tablets include FD&C Blue #1 Aluminum Lake and D&C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY

Hydrocodone is a semi-synthetic narcotic analgesic and antitussive with multiple action qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

= Brand Name / Generic Name

[redacted] = change due to dosage form

ANDA Product

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Listed Drug

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See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen tablets are indicated for the relief of moderate to moderate severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivit to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dos related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodon also affects the center that controls respiratory rhythm, and may produce irregular and period breathing.

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Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis clinical course of patients with acute abdominal conditions.

= Brand Name
Generic Name

ANDA Product

Listed Drug

PRECAUTIONS

General: Special Risk Patients: As with any opioid analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

PRECAUTIONS

General: Special Risk Patients: As with any opioid analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

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= Brand Name / Generic Name

ANDA Product

Pregnancy:
Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Listed Drug

Pregnancy:

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to deliver will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

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Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:
Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

= Brand Name / Generic Name

ANDA Product

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:
Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Listed Drug

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention ha been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respirato depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophe allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may deve upon repeated administration of narcotics; therefore, this product should be prescribed a administered with caution. However, psychic dependence is unlikely to develop when hydrocodo bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is requir to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportio only after several weeks of continued narcotic use, although some mild degree of physi dependence may develop after a few days of narcotic therapy. Tolerance, in which increasing large doses are required in order to produce the same degree of analgesia, is manifested initia by a shortened duration of analgesic effect, and subsequently by decreases in the intensity analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis, extre

= Brand Name / Generic Nam

ANDA Product

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 – 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Listed Drug

somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, an sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necros is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, an thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not b apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 gram or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentia lethal polydrug overdose, and consultation with a regional poison control center is recommended

Immediate treatment includes support of cardiorespiratory function and measures to reduc drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patien is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follo gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeate doses are used, the cathartic might be included with alternate doses as required. Hypotension usually hypovolemic and should respond to fluids. Vasopressors and other supportive measure should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastr lavage of the unconscious patient and, when necessary, to provice assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In sever cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administere intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated wi opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the durati of action of hydrocodone may exceed that of the naloxone, the patient should be kept und continuous surveillance and repeated doses of the antagonist should be administered as neede to maintain adequate respiration. A narcotic antagonist should not be administered in the absen of clinically significant respiratory or cardiovascular depression.

ANDA Product

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is two tablespoonfuls (30 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a clear, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 650 mg acetaminophen per 30 mL, with 7% alcohol. It is supplied as follows:

10mg/650 mg per 30 mL:	
16 oz. Bottles	NDC 0121-0718-16
4 oz. Bottles	NDC 0121-0718-04
30 mL Unit Dose Cups	NDC 0121-0718-30

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC

02/00

Listed Drug

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

2.5 mg/500 mg	The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
5 mg/500 mg	The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.
7.5 mg/500 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
7.5 mg/750 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.
7.5 mg/650 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
10 mg/500 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.
10 mg/650 mg	The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

Hydrocodone Bitartrate (WARNING: May be habit forming) and Acetaminophen Tablets are available in the following strengths:

2.5 mg/500 mg	2.5 mg hydrocodone bitartrate and 500 mg acetaminophen, oblong white tablets bisected on one side and debossed with Watson 388 on the other side.	
	Bottles of 30	NDC 52544-388-30
	Bottles of 100	NDC 52544-388-01
	Bottles of 500	NDC 52544-388-05
	Bottles of 1000	NDC 52544-388-10
5 mg/500 mg	5 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, white tablets bisected on one side and debossed with Watson 349 on the other side.	
	Bottles of 30	NDC 52544-349-30
	Bottles of 100	NDC 52544-349-01
	Bottles of 500	NDC 52544-349-05
7.5 mg/500 mg	7.5 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, white tablets bisected on one side and debossed with Watson 385 on the other side.	
	Bottles of 30	NDC 52544-385-30
	Bottles of 100	NDC 52544-385-01
	Bottles of 500	NDC 52544-385-05
	Bottles of 1000	NDC 52544-385-10
7.5 mg/750 mg	7.5 mg hydrocodone bitartrate and 750 mg acetaminophen, oblong white tablets bisected on one side and debossed with Watson 387 on the other side.	
	Bottles of 30	NDC 52544-387-30
	Bottles of 100	NDC 52544-387-01
	Bottles of 500	NDC 52544-387-05
	Bottles of 1000	NDC 52544-387-10
7.5 mg/650 mg	7.5 mg hydrocodone bitartrate and 650 mg acetaminophen, capsule-shaped, pink tablets bisected on one side and debossed with Watson 502 on the other side.	
	Bottles of 100	NDC 52544-502-01
	Bottles of 500	NDC 52544-502-05
10 mg/500 mg	10 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, blue tablets bisected on one side and debossed with Watson 540 on the other side.	
	Bottles of 100	NDC 52544-540-01
	Bottles of 500	NDC 52544-540-05
10 mg/650 mg	10 mg hydrocodone bitartrate and 650 mg acetaminophen, capsule-shaped, light green tablets bisected on one side and debossed with Watson 503 on the other side.	
	Bottles of 100	NDC 52544-503-01
	Bottles of 500	NDC 52544-503-05

Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

Watson Laboratories
Corona, CA 91720

Revised December 15, 1997
13100-1

= Brand Name / Generic Name

[redacted] = changed due to dosage form

= Controlled Room Temperature changed to current USP 24

Exhibit D

ANDA Product

Listed Drug

FRONT OF LABEL:

NDC 0121-0716-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR **CIII**

10 mg/325 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7 %
R$_x$ ONLY
16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature 20° - 25° C (68° - 77° F)

NDC 52544-539-01

NORCO™ (C III)
hydrocodone* bitartrate and acetaminophen tablets, USP

10 mg/325 mg

EACH TABLET CONTAINS:
Hydrocodone Bitartrate, USP....10 mg
*(WARNING: May be habit forming)
Acetaminophen, USP.....325 mg

CAUTION: Federal law prohibits dispensing without prescription.

WATSON Laboratories, Inc. A Subsidiary of Watson Pharmaceuticals, Inc.

100 Tablets

Dispense in a tight, light-resistant container with a child-resistant closure.

USUAL ADULT DOSAGE:
One tablet every four to six hours, as needed for pain.

Total daily dosage should not exceed six tablets.

See insert for full prescribing information.

Keep this and all medication out of the reach of children.

Store at controlled room temperature 15°-30°C (59°-86°F).

13058

N 52544-539-01 1

LOT NO.: 53902X97
EXP.: 12/99

= Brand Name / Generic Name

= change due to dosage form

= Controlled Room Temperature changed to Current USP 24

ANDA Product

Listed Drug

FRONT OF LABEL:

NDC 0121-0718-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR **CIII**

10 mg/650 mg per 30 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 650 mg
Alcohol 7 %
R$_x$ ONLY
16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature 20° - 25° C (68° - 77° F)

WATSON LABORATORIES, INC.

NDC 52544-503-01
HYDROCODONE BITARTRATE and ACETAMINOPHEN TABLETS, USP
10 mg/650 mg
Each Tablet Contains:
Hydrocodone Bitartrate, USP ..... 10 mg
(Warning: May be habit forming)
Acetaminophen, USP ..... 650 mg
CAUTION: Federal law prohibits dispensing without prescription.
100 TABLETS

Dispense in a tight, light-resistant container with a child-resistant closure.
Usual Adult Dosage: One tablet every four to six hours, as needed for pain.
Total daily dosage should not exceed six tablets.
See insert for full prescribing information.
Keep this and all medication out of the reach of children.
Store at controlled room temperature 15°-30°C (59°-86°F).

Watson Laboratories, Inc.
Corona, CA 91720

12592

N 3 52544-503-01 2

Lot No.: 50308E99
Exp: 5/2001

[redacted] = Brand Name / Generic Name

[redacted] = change due to dosage form

= Controlled Room Temperature
changed to current USP 24

15 mL Unit Dose Cup

Delivers **15 mL**
NDC 0121-0717-15

Hydrocodone Bitartrate and Acetaminophen Elixir **CIII**

10 mg/500 mg per 15 mL
Alcohol 7%
Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

Delivers **30 mL**
NDC 0121-0718-30

Hydrocodone Bitartrate and Acetaminophen Elixir **CIII**

10 mg/650 mg per 30 mL
Alcohol 7%
Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

15 mL Unit Dose Cup

Delivers **15 mL**
NDC 0121-0716-15

Hydrocodone Bitartrate and Acetaminophen Elixir

CIII

10 mg/325 mg per 15 mL
Alcohol 7%
Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

Delivers **15 mL**
NDC 0121-0715-15

Hydrocodone Bitartrate and Acetaminophen Elixir

CIII

10 mg/325 mg per 15 mL
Alcohol 7%
Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

NDC 0121-0717-15

HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR

10 mg/500 mg per 15 mL
Alcohol 7%
Preservative: Methylparaben 0.15%
pH Range: 4.0 – 5.0

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.
10 × 15 mL
This unit-dose package is not child-resistant.
Store at controlled room temperature,
20° - 25° C (68° - 77° F)
R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

NDC 0121-0718-30

HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR

10 mg/ 650 mg per 30 mL
Alcohol 7%
Preservative: Methylparaben 0.15%
pH Range: 4.0 – 5.0

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.
10 × 30 mL
This unit-dose package is not child-resistant.
Store at controlled room temperature,
20° - 25° C (68° - 77° F)
R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

NDC 0121-0716-15

HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR

10 mg/325 mg per 15 mL
Alcohol 7%
Preservative: Methylparaben 0.15%
pH Range: 4.0 – 5.0

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.
10 × 15 mL
This unit-dose package is not child-resistant.
Store at controlled room temperature,
20° - 25° C (68° - 77° F)
R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605
NDC 0121-0715-15

HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR

10 mg /325mg per 15 mL
Alcohol 7%
Preservative: Methylparaben 0.15%
pH Range: 4.0 – 5.0

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.
10 × 15 mL
This unit-dose package is not child-resistant.
Store at controlled room temperature,
20° - 25° C (68° - 77° F)
R_x ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605 NDC 0121-0715-15

FRONT OF LABEL:

NDC 0121-0717-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg /500 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 500 mg
Alcohol 7 %
R_x ONLY
16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

16 oz. Bottle

FRONT OF LABEL:

NDC 0121-0716-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg /325 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7 %
R_x ONLY
16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

16 oz. Bottle

FRONT OF LABEL:

NDC 0121-0715-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg /325 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7 %
R_x ONLY
16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

16 oz. Bottle

FRONT OF LABEL:

NDC 0121-0718-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg /650 mg per 30 mL

Hydrocodone bitartrate, USP	10 mg
(Warning: May be habit forming)	
Acetaminophen, USP	650 mg

Alcohol 7 %

R_x ONLY

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature 20° - 25° C (68° - 77° F)

FRONT OF LABEL:

NDC 0121-0717-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR **CIII**

10 mg /500 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 500 mg
Alcohol 7 %
R_x ONLY
4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

4 oz. Bottle Label

FRONT OF LABEL:

NDC 0121-0716-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR **CIII**

10 mg /325 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7 %
R_x ONLY
4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

FRONT OF LABEL:

NDC 0121-0715-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR **CIII**

10 mg /325 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7 %
R_x ONLY
4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

4 oz. Bottle Label

FRONT OF LABEL:

NDC 0121-0718-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR **CIII**

10 mg /650 mg per 30 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 650 mg
Alcohol 7 %
R_x ONLY
4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

Exhibit E

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0715-) has been packaged in the following container/closure systems:

1. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

2. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner

3. Bottle: 16 oz. Brown HDPE BL-16 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

6. Bottle: 4 oz. Amber PET 24-400 container
   Cap: 24-400 White Clic-Loc with P/RVTLF Liner

7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin.
   Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0716-) has been packaged in the following container/closure systems:

1. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

2. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner

3. Bottle: 16 oz. Brown HDPE BL-16 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

6. Bottle: 4 oz. Amber PET 24-400 container
   Cap: 24-400 White Clic-Loc with P/RVTLF Liner

7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin.
   Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0717-) has been packaged in the following container/closure systems:

1. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

2. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner

3. Bottle: 16 oz. Brown HDPE BL-16 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

6. Bottle: 4 oz. Amber PET 24-400 container
   Cap: 24-400 White Clic-Loc with P/RVTLF Liner

7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin.
   Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0718-) has been packaged in the following container/closure systems:

1. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

2. Bottle: 16 oz. Amber PET 28-400 container
   Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner

3. Bottle: 16 oz. Brown HDPE BL-16 container
   Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner

6. Bottle: 4 oz. Amber PET 24-400 container
   Cap: 24-400 White Clic-Loc with P/RVTLF Liner

7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin.
   Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.

PHARMACEUTICAL ASSOCIATES INC

201 DELAWARE STREET
GREENVILLE SC 29605

1 OF 1

SHIP TO: DOCKETS MANAGEMENT
HFA-305
FOOD & DRUG ADMIN
5600 FISHER LANE,RI
ROCKVILLE,MD

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(420) 20857

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